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APPEAL BRIEF - PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	H. Lowenheim	Attorney Docket No.:	SOPH116953
Application No.:	09/622,719	Group Art Unit:	1635/ Confirmation No. 1261
Filed:	October 18, 2000	Examiner:	T.A. Vivlemore
Title:	METHOD FOR THE TREATMENT OF DISEASES OR DISORDERS OF THE INNER EAR		

RESPONSE TO NOTIFICATION OF
NON-COMPLIANT APPEAL BRIEF (37 C.F.R. 41.37)

Seattle, Washington 98101

December 15, 2005

TO THE COMMISSIONER FOR PATENTS:

This paper is filed in reply to the Notification of Non-compliant Appeal Brief dated December 1, 2005. A Revised Appeal Brief is attached.

With regard to Items 8 and 10, the Examiner indicates that the brief does not contain the required statement in the appendix setting forth where, in the record, evidence submitted under 37 CFR 1.130, 1.131 or 1.132 and relied upon by the applicant was entered by the Examiner. Applicant has revised Section IX to include the required statements setting forth the places in the record where the Examiner entered the cited evidence.

Applicant apologizes for any inconvenience the foregoing may have caused the Office.

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If the Examiner has any further questions or comments, she is invited to call applicant's attorney at the number listed below. Otherwise, it is believed that the Revised Appeal Brief conforms to the new appeal rules as set forth in 37 C.F.R. 41.37.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

Date: December 15, 2005

TJQ:pt

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MAIL STOP APPEAL

BRIEF - PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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Application No:	09/622,719	Group Art Unit: 1635 / Confirmation No.: 1261
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APPELLANT'S APPEAL BRIEF

Seattle, Washington
December 15, 2005

TO THE COMMISSIONER FOR PATENTS:

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I. REAL PARTY IN INTEREST

Sound Pharmaceuticals Incorporated, a Washington corporation, having a place of business at 4010 Stone Way N., Suite 120, Seattle, Washington 98103, is the assignee of the entire interest of the appealed subject matter.

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II. RELATED APPEALS AND INTERFERENCES

There are none.

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III. STATUS OF CLAIMS

Claims 28, 31, and 63 are pending in the application. All stand rejected under 35 U.S.C. § 112, first paragraph. Claims 28, 31, and 63 are appealed. The table below indicates their status.

Claim(s)	Status	Appealed
1-27	Canceled	No
28	Rejected	Yes
29-30	Canceled	No
31	Rejected	Yes
32-62	Canceled	No
63	Rejected	Yes
64-66	Canceled	No

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IV. STATUS OF AMENDMENTS

The application was rejected in an Office Action dated September 10, 2002. Thereafter, an Amendment and Response to the non-final Office Action was mailed on March 7, 2003, and entered into the file. An additional non-final Office Action was mailed on June 4, 2003. A further Amendment and Response to this Office Action was mailed on November 4, 2003, and entered into the file. The application was finally rejected in a paper dated February 13, 2004. An Amendment and Response After Final was mailed on May 11, 2004, but was not entered into the file. An Advisory Action was mailed on May 25, 2004. Thereafter, an Amendment and Response, together with a Request for Continued Examination, was mailed on June 9, 2004, and entered into the file. The application was again rejected in an Office Action dated July 2, 2004. Thereafter, a Response to Office Action was mailed on December 29, 2004, and entered into the file. The application was again finally rejected in a paper dated March 15, 2005. A copy of the pending claims is attached in the Claims Appendix.

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V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to a process for the treatment of disease or disorders of the inner ear, which are caused by damage or destruction of the sensory cells of the inner ear. (See instant Specification, page 1, first paragraph.) Prior to the present invention, it was not possible to regenerate irreversibly damaged cells in the highly differentiated sensory epithelia in the inner ear of humans and other mammals. Thus, a partial or complete hearing loss due to damage or destruction of the sensory cells of the inner ear was generally irreversible. (See instant Specification, page 1, third paragraph.)

Inner ear sensory cells are located upon a layer of supporting cells. The supporting cells do not normally divide or regenerate in adult mammals. (See, e.g., instant Specification, page 2, second paragraph.) In the practice of the present invention, one or more cell cycle inhibitors in the supporting cells of the inner ear are inhibited, or eliminated, so that the supporting cells re-enter the cell cycle and divide, thereby creating cells which can differentiate to form new sensory cells and supporting cells. (See instant Specification, page 3, second paragraph.) The cell cycle inhibitor that is targeted in the practice of the currently claimed invention is a member of the so-called cyclin-dependent kinase inhibitors, called $p27^{kip1}$. (See instant Specification, page 4, second paragraph.)

In the practice of the currently claimed invention, antisense molecules are used to inhibit $p27^{kip1}$ synthesis. The antisense molecules are short nucleic acid molecules (sometimes referred to as oligonucleotides) that bind to mRNA that encodes $p27^{kip1}$, thereby blocking the synthesis of $p27^{kip1}$ in cells. (See instant Specification, page 5, second paragraph.)

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VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

First Ground of Rejection - Claims 28, 31, and 63

Claims 28, 31, and 63 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

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VII. ARGUMENT

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 28, 31, and 63

The Examiner argues that Claims 28, 31 and 63 are drawn to methods that require antisense molecules targeted to any mammalian $p27^{kip1}$. The Examiner states that the specification does not disclose the structure (i.e. nucleotide sequence) of any antisense molecules targeted to mammalian $p27^{kip1}$, nor does it disclose the target sequences for any mammalian $p27^{kip1}$ or the common structural elements (e.g. regions of homology) for mammalian $p27^{kip1}$. The Examiner notes that the prior art at the time of the invention provided two antisense molecules targeted to one species of mammalian $p27^{kip1}$ (human $p27^{kip1}$) and disclosed the nucleotide sequence encoding three species of mammalian $p27^{kip1}$.

The Examiner further argues that the genus of mammalian $p27^{kip1}$ is broad, encompassing any mammalian organism and the species encompassed within the genus are highly variant (for example, with regard to nucleotide sequence.) The Examiner notes that, at the time of the invention, $p27^{kip1}$ from three mammals was known in the prior art, however, according to the Examiner, knowledge of three homologs of $p27^{kip1}$ is not sufficient to describe all homologs of $p27^{kip1}$ from all mammals. According to the Examiner, the specification does not correct the deficiencies of the prior art, because the prior art does not describe any homologs of $p27^{kip1}$ from any other mammal.

As a preliminary matter, applicant respectfully disagrees with the Examiner's assertion that the species encompassed by the genus of mammalian $p27^{Kip1}$ molecules is highly variant, for example with regard to nucleotide sequence. Applicant submits that, on the contrary, the art teaches that the species encompassed within the genus of mammalian nucleic acid molecules encoding $p27^{Kip1}$ proteins have highly related sequences. For example, in the response

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submitted on June 9, 2004, together with the Request for Continued Examination, applicant provided a Clustal W Alignment of the nucleic acid sequences encoding human, mouse, and mink $p27^{Kip1}$ proteins. The nucleic acid sequences encoding human, mouse, and mink $p27^{Kip1}$ proteins have been publicly available under GenBank accession numbers U10906, U09968 and U09966, respectively, since July 27, 1994. This alignment showed that these three nucleic acid sequences are more than 85% identical. A copy of the Clustal W Alignment is submitted herewith as Attachment A in the Evidence Appendix. Further, as described by Polyak et al. (*Cell 78*:59-66 (1994)), which was made of record in the response dated November 4, 2003, the $p27^{Kip1}$ proteins encoded by these nucleic acid molecules are about 90% identical (Polyak et al., page 61, last line, to page 62, line 2). A copy of the Polyak et al. publication is submitted herewith as Attachment B in the Evidence Appendix.

In the Office Action mailed March 15, 2005, in the section entitled "Response to Arguments", the Examiner states that,

> Applicant argues that the Examiner has not provided a basis for stating the genus of $p27^{Kip1}$ is variant with regard to nucleotide sequences and refers to previous arguments demonstrating 85 % homology between the three known mammalian $p27^{Kip1}$. This is not persuasive as this demonstrates that the known mammalian $p27^{Kip1}$ have variability of 15 %.

Applicant submits that sequences that are more than 85 % identical are highly related and homologous. Indeed, Applicant notes that the Court of Appeals for the Federal Circuit recognizes that nucleic acid sequences that are more than 85 % identical are highly homologous. For example, in *Enzo Biochem, Inc. v. GenProbe, Inc.*, (296 F.3d 1316, 63 U.S.P.Q. 2d 1609 (Fed. Cir. 2002)) the Court of Appeals for the Federal Circuit described the background to the case as follows:

> Enzo is the assignee of the '659 patent, which is directed to nucleic acid probes that selectively hybridize to the genetic material of the bacteria that cause gonorrhea, *Neisseria gonorrhoeae*. *N. gonorrhoeae* reportedly has

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> between eighty and ninety three percent homology with *Neisseria meningitidis*. '659 patent, col. 2, 11. 61-64. Such a high degree of homology has made detection of *N. gonorrhoeae* difficult, as any probe capable of detecting *N. gonorrhoeae* may also show a positive result when only *N. meningitidis* is present. *Enzo Biochem, Inc.*, 296 F.3d at 1320-1321, 63 U.S.P.Q. 2d at 1610. [Underline added.]

Thus, Applicant submits that the art teaches that the species encompassed by the genus of nucleic acid molecules encoding mammalian $p27^{Kip1}$ proteins are highly conserved and homologous.

With respect to the Examiner's argument that the instant specification, and the prior art, do not adequately describe the genus of nucleic acid molecules that encode a $p27^{kip1}$, Applicant notes that the written description requirement may be satisfied if in the knowledge in the art the disclosed function is sufficiently correlated to a particular, known, structure. *Amgen Inc., v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332, 65 U.S.P.Q. 2d 1385, 1398 (Fed. Cir. 2003), citing *Enzo Biochem* 296 F.3d at 1324, 63 U.S.P.Q. 2d at 1398.

Applicant submits that the prior art discloses the nucleic acid sequences of mRNAs encoding human, mouse, and mink $p27^{Kip1}$ proteins (publicly available under GenBank accession numbers U10906, U09968 and U09966, respectively). As shown in the attached Clustal W alignment (Attachment A), the nucleic acid sequences of these three $p27^{Kip1}$ mRNAs are highly conserved. Applicant submits that it can be reasonably inferred that other mRNAs that encode a mammalian $p27^{Kip1}$ protein are highly conserved. Thus, Applicant submits that the function of encoding a $p27^{Kip1}$ protein is correlated with highly conserved nucleic acid sequences. Applicant submits, therefore, that the prior art has adequately described the genus of nucleic acid molecules that encode a mammalian $p27^{Kip1}$.

With respect to the $p27^{Kip1}$ antisense nucleic acid molecules, Applicant submits that the written description requirement is satisfied because knowledge of the sequence of a single member of the highly conserved family of $p27^{Kip1}$ genes is sufficient to allow one of ordinary

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skill in the art to make effective $p27^{Kip1}$ antisense nucleic acid molecules. As described more fully below, inventor Jonathan Kil made fourteen effective $p27^{Kip1}$ antisense nucleic acid molecules. The antisense nucleic acid molecules each corresponded to a different sequence within the first 445 bases of the target $p27^{Kip1}$ mRNA. Thus, one of ordinary skill in the art can readily determine the sequence of an effective $p27^{Kip1}$ antisense molecule by selecting a portion of a nucleic acid molecule that encodes $p27^{Kip1}$.

The antisense experiments conducted by Jonathan Kil are described in the declaration (referred to as the Third Kil Declaration) filed with the response dated December 29, 2004. A copy of the Third Kil Declaration is submitted herewith as Attachment C in the Evidence Appendix. A copy of Dr. Kil's *Curriculum vitae* is submitted herewith as Attachment D in the Evidence Appendix, and was made of record in the response dated June 9, 2004. The Third Kil Declaration describes the results of experiments in which 14 antisense oligonucleotides (directed against mouse $p27^{Kip1}$ mRNA) were introduced into mouse NIH 3T3 cells, cultured *in vitro*, and subsequently the level of $p27^{Kip1}$ mRNA was measured.

The nucleic acid sequences of the 14 antisense oligonucleotides are set forth in Table 1, paragraph 3, of the Third Kil Declaration. As described in paragraph 3 of the Third Kil Declaration, the location of each oligonucleotide is given with reference to the sequence of the mouse $p27^{Kip1}$ cDNA (GenBank accession number U09968; reported in Polyak, K., et al, *Cell 78*: 56-66 (1994)).

As described in paragraph 3 of the Third Kil Declaration, the cells were incubated in the presence of the oligonucleotide for 26 hours. Real time PCR was used to measure the amount of $p27^{Kip1}$ mRNA present in total RNA extracted from the treated cells.

Enclosed herewith as Attachment E is a graph showing the level of $p27^{Kip1}$ mRNA in the cells treated with the different oligonucleotides, compared to the control level of $p27^{Kip1}$ mRNA

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in cells treated with the Lipofectamine lipid delivery vehicle without oligonucleotides. A copy of this graph was filed with the response dated December 29, 2004. As described in paragraph 4 of the Third Kil Declaration, the results shown in the graph (which is referred to as Attachment B in the Third Kil Declaration) demonstrate that all of the tested oligonucleotides caused a significant reduction in the level of $p27^{Kip1}$ mRNA in the treated cells.

As can be seen from Table 1 of the Third Kil Declaration, the antisense oligonucleotides each corresponded to a different sequence within the first 445 bases of the $p27^{Kip1}$ mRNA. Thus, the results of these experiments are consistent with the view that the level of expression of a $p27^{Kip1}$ mRNA can be significantly reduced by an antisense oligonucleotide that corresponds to any sequence of at least 14 consecutive nucleotides within a $p27^{Kip1}$ mRNA. Applicant submits, therefore, that the written description requirement is satisfied by the existence, in the prior art, of the nucleic acid sequence of at least one member of the highly conserved genus of mammalian $p27^{Kip1}$ mRNAs (e.g., the sequence of the mouse $p27^{Kip1}$ cDNA, set forth in the GenBank database as accession number U09968, which was reported by Polyak et al. in 1994) that can be used as a source of antisense oligonucleotide sequences.

Consequently, Applicant requests withdrawal of the rejection of Claims 28, 31, and 63 under 35 U.S.C. § 112, first paragraph.

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VIII. CLAIMS APPENDIX

1-27. (Canceled)

28. (Currently Amended) A process for the treatment of hearing loss caused by damaged inner ear sensory hair cells, the process comprising the step of at least partly inhibiting or eliminating the action of $p27^{Kip1}$ present in the inner ear by local administration of antisense molecules to mammalian $p27^{Kip1}$ to the inner ear, thereby promoting regeneration of the sensory hair cells of the inner ear.

29-30. (Canceled)

31. (Previously presented) The process according to claim 28, characterized in that the regeneration of the sensory cells of the inner ear takes place by stimulating proliferation of the supporting cells of the inner ear.

32-62. (Canceled)

63. (Currently amended) A process for promoting regeneration and growth of sensory hair cells in the inner ear of a mammalian subject in need thereof, the process comprising the step of locally administering antisense molecules to mammalian $p27^{Kip1}$ to the inner ear in an amount sufficient to promote regeneration and growth of sensory hair cells in the inner ear.

64-66. (Canceled)

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IX. EVIDENCE APPENDIX

Appendix A	Clustal W Alignment This evidence was submitted by the applicants on June 9, 2004 and was entered into the record by the Examiner in the Non-final Office Action dated July 2, 2004.
Appendix B	Polyak et al., *Cell 78*:59-66, 1994 This reference was submitted by the applicants on November 4, 2003, and was considered by the Examiner in the Final Office Action dated February 13, 2004.
Appendix C	Third Kil Declaration This evidence was submitted by the applicants on December 29, 2004, and was entered into the record by the Examiner in the Final Office Action dated March 15, 2005.
Appendix D	*Curriculum vitae* of Dr. Jonathan Kil This evidence was submitted by the applicants on June 9, 2004 and was entered into the record by the Examiner in the Non-final Office Action dated July 2, 2004.
Appendix E	Graph showing the level of p27Kip1 mRNA in cells treated with different oligonucleotides This evidence was submitted by the applicants on December 29, 2004, and was entered into the record by the Examiner in the Final Office Action dated March 15, 2005.

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X. RELATED PROCEEDINGS APPENDIX

None.

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